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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/594,876	09/29/2006	Hannsjorg Sinn	14836-56813	3262

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EXAMINER	
RUSSEL, JEFFREY E	

ART UNIT	PAPER NUMBER
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/594,876	SINN, HANNSJORG	
	Examiner	Art Unit	
	Jeffrey E. Russel	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 September 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20060929*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration filed September 29, 2008 is defective because it is not in the English language, and was not accompanied by an English translation together with a statement that the translation is accurate, as is required by 37 CFR 1.69(b). See also 37 CFR 1.497(c) and MPEP 602.06.

2. The abstract of the disclosure is objected to because it is insufficiently detailed with respect to the type of active substance, the type of protein, and how the conjugates are formed from the active substance and the protein. Further, legal terminology present in the abstract, e.g., "novel" and "according to the invention", should be omitted. Correction is required. See MPEP § 608.01(b).

3. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-14 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. A "use" is not a statutory class of invention.

4. Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is not clear what constitutes a "use" as is recited in instant claims 1-14. It is not clear if Applicant is claiming, e.g., a product with an intended use limitation, or a method of use. To the extent that the latter is intended, the claims are indefinite because they are drawn to a method, but no positive process steps are recited. The "in particular…" phrases recited in instant

claims 7, 11, 19, and 20 are indefinite because it is not clear if the scopes of the claims are to be limited to the particular embodiments or not. It is suggested that the "in particular..." phrases could be deleted and made the subject matter of further dependent claims. The significance of the conjunction "and/or" in claims 10 and 17, in contrast to the conjunction "or" which is used in other Markush groups appearing in the claims, is not understood. Claims 11 and 19 are indefinite because it is not clear if the molar ratio is referring to the ratio of the compound and the albumin as reactants, or to the ratio of the compound and the albumin in the conjugate product. At claim 15, line 4, "a" should be changed to "the" so that it is clear that the claim is referring to the carboxyl group-containing organic compound and the albumin of parts i) and ii). There is no antecedent basis in the claims for the phrase "the protein" at claim 20, line 5. It is believed the phrase should be changed to "the albumin".

5. Claims 11 and 19 are objected to because of the following informalities: At claim 11, line 2, and claim 19, line 2, "organic" should be inserted before "compound", consistent with the terminology used elsewhere in the claims. Appropriate correction is required.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

For the purposes of this invention, the level of ordinary skill in the art is deemed to be at least that level of skill demonstrated by the patents in the relevant art. Joy Technologies Inc. v. Quigg, 14 USPQ2d 1432 (DC DC 1990). One of ordinary skill in the art is held accountable not only for specific teachings of references, but also for inferences which those skilled in the art may reasonably be expected to draw. In re Hoeschele, 160 USPQ 809, 811 (CCPA 1969). In addition, one of ordinary skill in the art is motivated by economics to depart from the prior art to reduce costs consistent with desired product properties. In re Clinton, 188 USPQ 365, 367 (CCPA 1976); In re Thompson, 192 USPQ 275, 277 (CCPA 1976).

7. Claims 1-18 are rejected under 35 U.S.C. 102(b) as being anticipated by the Bures et al article (Neoplasma, Vol. 35, pages 329-342). The Bures et al article teaches forming a conjugate between human serum albumin and methotrexate in the presence of 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide. See, e.g., page 329, first paragraph, and page 331, ninth full paragraph. With respect to instant claims 1-14, an intended use limitation does not impart patentability to product claims where the product is otherwise anticipated by the prior art. With respect to instant claim 11, assuming that this claim specifies the molar ratio of the reactants (see the above rejection under 35 U.S.C. 112, second paragraph, and see also page 11, lines 13-17, of Applicant's specification), process limitations do not impart patentability to product-by-process claims where the product is otherwise anticipated by or obvious over the prior art.

8. Claim 19 is rejected under 35 U.S.C. 103(a) as being obvious over the Bures et al article (Neoplasma, Vol. 35, pages 329-342). Application of the Bures et al article is the same as in the above rejection of claims 1-18. The Bures et al article does not teach a molar ratio of methotrexate and albumin reactants of from 10:1 to 1:10. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to determine all operable and optimal molar ratios for the methotrexate and albumin reactants of the Bures et al article, because reactant ratio is an art-recognized result-effective variable which is routinely determined and optimized in the chemical arts.

9. Claims 1-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Sutton et al (U.S. Patent No. 5,993,805). Sutton et al teach adding EDCI to a solution of methotrexate, stirring to ensure initiation and complete activation of the methotrexate, and then adding HSA, whereby the methotrexate is bound to amine residues on the HSA. See, e.g., Example 12. With respect to instant claims 1-14, an intended use limitation does not impart patentability to product claims where the product is otherwise anticipated by the prior art. With respect to instant claim 11, assuming that this claim specifies the molar ratio of the reactants (see the above rejection under 35 U.S.C. 112, second paragraph, and see also page 11, lines 13-17, of Applicant's specification), process limitations do not impart patentability to product-by-process claims where the product is otherwise anticipated by or obvious over the prior art.

10. Claim 19 is rejected under 35 U.S.C. 103(a) as being obvious over Sutton et al (U.S. Patent No. 5,993,805). Application of Sutton et al is the same as in the above rejection of claims 1-18. Sutton et al do not teach a molar ratio of methotrexate and albumin reactants of from 10:1 to 1:10. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to determine all operable and optimal molar ratios for the methotrexate and albumin reactants of Sutton et al, because reactant ratio is an art-recognized result-effective variable which is routinely determined and optimized in the chemical arts.

11. Claim 20 is rejected under 35 U.S.C. 103(a) as being obvious over Sutton et al (U.S. Patent No. 5,993,805) as applied against claims 1-18 above, and further in view of the European Patent Application 0 282 057 or Low et al (U.S. Patent No. 5,688,488). Sutton et al teach reacting methotrexate with EDCI in solution, but do not specify the solvent. The European Patent Application '057 teaches activating methotrexate with EDCI for reacting with an antibody

carrier, wherein the activation reaction is carried out in dry DMF. Low et al teach that folic acid (of which methotrexate is an analog) can be activated by EDC in a DMSO solution. The activated folic acid is then reacted with a protein, ribonuclease. See, e.g., column 18, lines 47-50. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to perform the activation reaction of Sutton et al using the dry DMF solvent of the European Patent Application '057 or the DMSO solvent of Low et al, because the European Patent Application '057 teaches that dry DMF is a known solvent for performing the activation reaction of Sutton et al, because Low et al teach that DMSO is a known solvent for performing the activation reaction of a compound analogous to methotrexate, and because substitution of one known reaction solvent for another with only the expected result that methotrexate is activated by EDCI is prima facie obvious. With respect to the "activated by heating" step recited in claim 20, the claim does not specify any particular degree of heating. However, Applicant's specification at page 8, lines 36-37, states that activation can occur at temperatures ranging from 10°C to 100°C, which embraces room temperatures. Sutton et al do not disclose a temperature for their step of reacting methotrexate with EDCI, and therefore it is presumed to occur at room temperature and satisfies Applicant's claim limitation. In any event, it would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to determine all operable and optimal temperatures for Sutton et al's step of reacting methotrexate with EDCI, because reaction temperature is an art-recognized result-effective variable which is routinely determined and optimized in the chemical arts.

12. The Shen et al article (PNAS, Vol. 81, pages 1445-1447) is cited as art of interest, being essentially duplicative of the Bures et al article applied above.

Bohannon (U.S. Patent No. 6,210,677) is cited as art of interest, showing the coupling of drugs, including methotrexate, to carrier molecules, including albumin, using EDC. See, e.g., Example 3.

The Wolff et al abstract (Blood, Vol. 102, No. 11, page 404b), cited in the International Search Report, teaches the use of methotrexate-human serum conjugates to prevent, although not to treat, experimental acute GVHD.

Fatih (U.S. Patent Application Publication 2003/0149045 - see, e.g., paragraph [0304]) and McDonald et al (U.S. Patent Application Publication 2003/0032631 - see, e.g., paragraph [0006]) are cited as art of interest, teaching that methotrexate is a standard anti-GVHD drug.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (571) 272-0969. The examiner can normally be reached on Monday-Thursday from 8:00 A.M. to 5:30 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Cecilia Tsang can be reached at (571) 272-0562. The fax number for formal communications to be entered into the record is (571) 273-8300; for informal communications such as proposed amendments, the fax number (571) 273-0969 can be used. The telephone number for the Technology Center 1600 receptionist is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Jeffrey E. Russel/
Primary Examiner, Art Unit 1654

JRussel
May 5, 2008